In the Specification

Please substitute the following Title of the invention on page 1, beginning at line 1:

~~HUMAN GDNAS AND PROTEINS AND USES THEREOF~~

vCOL16A1 POLYPEPTIDES

Please substitute the following paragraph on page 33, beginning at line 26 through to page 34, line 16:

The probes of the present invention are useful for a number of purposes. They can notably be used in Southern hybridization to genomic DNA. The probes can also be used to detect PCR amplification products. They may also be used to detect mismatches in the GENSET gene or mRNA using other techniques. They may also be used to in situ hybridization. Any of the polynucleotides, primers and probes of the present invention can be conveniently immobilized on a solid support. The solid support is not critical and can be selected by one skilled in the art. Thus, latex particles, microparticles, magnetic beads, non-magnetic beads (including polystyrene beads), membranes (including nitrocellulose strips), plastic tubes, walls of microtiter wells, glass or silicon chips, sheep (or other suitable animal's) red blood cells and ~~duracytes~~ DURACYTES are all suitable examples. Suitable methods for immobilizing nucleic acids on solid phases include ionic, hydrophobic, covalent interactions and the like. A solid support, as used herein, refers to any material which is insoluble, or can be made insoluble by a subsequent reaction. The solid support can be chosen for its intrinsic ability to attract and immobilize the capture reagent. Alternatively, the solid phase can retain an additional receptor which has the ability to attract and immobilize the capture reagent. The additional receptor can include a charged substance that is oppositely charged with respect to the capture reagent itself or to a charged substance conjugated to the capture reagent. As yet another alternative, the receptor molecule can be any specific binding member which is immobilized upon (attached to) the solid support and which has the ability to immobilize the capture reagent through a specific binding reaction. The receptor molecule enables the indirect binding of the capture reagent to a solid support material before the performance of the assay or during the performance of the assay. The solid phase thus can be a plastic, derivatized plastic, magnetic or non-magnetic metal,

glass or silicon surface of a test tube, microtiter well, sheet, bead, microparticle, chip, sheep (or other suitable animal's) red blood cells, ~~duracytes®~~ DURACYTES and other configurations known to those of ordinary skill in the art. The polynucleotides of the invention can be attached to or immobilized on a solid support individually or in groups of at least 2, 5, 8, 10, 12, 15, 20, or 25 distinct polynucleotides of the invention to a single solid support. In addition, polynucleotides other than those of the invention may be attached to the same solid support as one or more polynucleotides of the invention.

Please substitute the following paragraph on page 44, beginning at line 27:

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al., (1994), FEBS Letters. 344:191 and in U.S. patent application Ser. No. 08/446,922, which disclosure is hereby incorporated by reference in its entirety. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention. In another example, proteins of the invention are associated by interactions between ~~Flag®~~ FLAG polypeptide sequence contained in fusion proteins of the invention containing ~~Flag®~~ FLAG polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in ~~Flag®~~ FLAG fusion proteins of the invention and anti-~~Flag®~~ FLAG antibody.

Please substitute the following paragraph on page 178, beginning at line 12 through to page 179, line 10:

These embodiments comprise methods for detection of RET-A-MODULIN-mediated proliferation inhibition and apoptosis including in vitro activity tests of RET-A-MODULIN or other proteins of the invention or fragments thereof, further cellular proliferation assays, and cellular apoptosis/necrosis assays. Specific examples of apoptosis assays are also provided in the following references. Assays for apoptosis in lymphocytes are disclosed by Noteborn et al., US Patent 5,981,502, 1999, Li et al., "Induction of apoptosis in uninfected lymphocytes by HIV-1 Tat protein",

Science 268: 429-431, 1995; Gibellini et al., "Tat-expressing Jurkat cells show an increased resistance to different apoptotic stimuli, including acute human immunodeficiency virus-type 1 (HIV-1) infection", Br. J. Haematol. 89: 24-33, 1995; Martin et al., "HIV-1 infection of human ~~CD4 sup.+~~ CD4$^+$ T cells in vitro. Differential induction of apoptosis in these cells." J. Immunol. 152:330-342, 1994; Terai et al., "Apoptosis as a mechanism of cell death in cultured T lymphoblasts acutely infected with HIV-1", J. Clin Invest. 87: 1710-1715, 1991; Dhein et al., "Autocrine T-cell suicide mediated by APO-1/(Fas/CD95)", Nature 373: 438-441, 1995; Katsikis et al., "Fas antigen stimulation induces marked apoptosis of T lymphocytes in human immunodeficiency virus-infected individuals", J. Exp. Med. 1815:2029-2036, 1995; Westendorp et al., "Sensitization of T cells to CD95-mediated apoptosis by HIV-1 Tat and gp120", Nature 375:497, 1995; DeRossi et al, Virology 198:234-244, 1994. Assays for apoptosis in fibroblasts are disclosed by: Vossbeck et al, "Direct transforming activity of TGF-beta on rat fibroblasts", Int. J. Cancer 61:92-97, 1995; Goruppi et al., "Dissection of c-myc domains involved in S phase induction of NIH3T3 fibroblasts", Oncogene 9:1537-44, 1994; Fernandez et al, "Differential sensitivity of normal and Ha-ras transformed C3H mouse embryo fibroblasts to tumor necrosis factor: induction of bcl-2, c-myc, and manganese superoxide dismutase in resistant cells", Oncogene 9:2009-2017, 1994; Harrington et al., "c-Myc-induced apoptosis in fibroblasts is inhibited by specific cytokines", EMBO J. 13:3286-3295, 1994; Itoh et al., "A novel protein domain required for apoptosis. Mutational analysis of human Fas antigen", J. Biol. Chem. 268;10932-10937, 1993. In vitro cellular proliferation assays comprise cultured cells such as Jurkat, HepG2, K562, or HeLa, which are treated with RET-A-MODULIN or fragments thereof at concentration ranges for example from 0.5 to 25 ug/mL, and percent decrease in cellular proliferation is measured 24, 48, and 72 hours after treatment. Cellular apoptosis is measured using an apoptosis assay kit such as ~~VYBRANT™~~ VYBRANT Apoptosis Assay Kit #3 (Molecular Probes). After harvesting and washing, cells are stained with a FITC-labeled anti-RET-A-MODULIN antibody and analyzed by FACS according to manufacturer's instructions. Cells will be stained with PI or DAPI to detect apoptotic nuclei. DNA fragmentation analysis will be performed by cellular DNA extraction and Southern blot analysis using about 1 ug of DNA and hybridized with randomly primed ^{32}P-labeled chromosomal DNA from said cells, which had not been treated, with RET-A-MODULIN.

Please substitute the following paragraphs on page 188, beginning at line 25 through to page 191, line 4:

In yet another preferred embodiment, Tifapinix or fragments thereof are used for in vitro diagnostic methods and reagents. Tifapinix and related sequences may be applied in vitro to any suitable sample that might contain plasmin to measure the plasmin present. The assay must include a Signal Producing System (SPS) providing a detectable signal that depends on the amount of plasmin present. The signal may be detected visually or instrumentally. Possible signals include production of colored, fluorescent, or luminescent products, alteration of the characteristics of absorption or emission of radiation by an assay component or product, and precipitation or agglutination of a component or product. The component of the SPS most intimately associated with the diagnostic reagent is called the "label". A label may be, e.g., a radioisotope, a fluorophore, an enzyme, a co-enzyme, an enzyme substrate, an electron-dense compound, or an agglutinable particle. A radioactive isotope can be detected by use of, for example, a .gamma. counter or a scintillation counter or by autoradiography. Isotopes which are particularly useful are ~~.sup.3~~H[3]H, ~~.sup.125~~I[125]I, ~~.sup.131~~I[131]I, ~~.sup.35~~S[35]S, ~~.sup.14~~C[14]C, and, preferably, ~~.sup.125~~I[125]I. It is also possible to label a compound with a fluorescent compound. When the fluorescent-labeled compound is exposed to light of the proper wavelength, its presence can be detected. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, and fluorescamine. Alternatively, fluorescence-emitting metals, such as ~~.sup.125~~Eu[125]Eu or other anthanide, may be attached to the binding protein using such metal chelating groups as diethylenetriaminepentaacetic acid or ethylenediamine-tetraacetic acid. The proteins also can be detectably labeled by coupling to a chemiluminescent compound, such as luminol, isolumino, theromatic acridinium ester, imidazole, acridinium salt, and oxalate ester. Likewise, a bioluminescent compound, such as luciferin, luciferase and aequorin, may be used to label the binding protein. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Enzyme labels, such as horseradish peroxidase and alkaline phosphatase, are preferred. There are two basic types of assays: heterogeneous and homogeneous. In heterogeneous assays, binding of the affinity molecule to analyte does not affect the label; thus, to determine the amount of analyte, bound label must be separated from free label. In homogeneous

assays, the interaction does affect the activity of the label, and analyte can be measured without separation. Tifapinix, as a plasmin-binding protein may be used diagnostically in the same way that an antiplasmin antibody is used. Thus, depending on the assay format, it may be used to assay plasmin, or, by competitive inhibition, other substances which bind plasmin. The sample will normally be a biological fluid, such as blood, urine, lymph, semen, milk, or cerebrospinal fluid, or a derivative thereof, or a biological tissue, e.g., a tissue section or homogenate. If the sample is a biological fluid or tissue, it may be taken from a human or other mammal, vertebrate or animal, or from a plant. The preferred sample is blood, or a fraction or derivative thereof. In a related embodiment, Tifapinix or fragments thereof is immobilized, and plasmin in the sample is allowed to compete with a known quantity of a labeled or specifically labelable plasmin analogue. The "plasmin analogue" is a molecule capable of competing with plasmin for binding to Tifapinix or fragments thereof. It may be labeled already, or it may be labeled subsequently by specifically binding the label to a moiety differentiating the plasmin analogue from plasmin. The phases are separated, and the labeled plasmin analogue in one phase is quantified. In a "sandwich assay", both an insolubilized plasmin-binding agent (PBA), and a labeled PBA are employed. The plasmin analyte is captured by the insolubilized PBA and is tagged by the labeled PBA, forming a tertiary complex. The reagents may be added to the sample in any order. The PBAs may be the same or different, and only one PBA needs to comprise Tifapinix or fragments thereof according to this invention (the other may be, e.g., an antibody). The amount of labeled PBA in the tertiary complex is directly proportional to the amount of plasmin in the sample. The two embodiments described above are both heterogeneous assays. A homogeneous assay requires only that the label be affected by the binding of Tifapinix or fragments thereof to plasmin. The plasmin analyte may act as its own label if Tifapinix or fragments thereof are used as a diagnostic reagent. A label may be conjugated, directly or indirectly (e.g., through a labeled anti-Tifapinix antibody), covalently (e.g., with SPDP) or noncovalently, to the plasmin-binding protein, to produce a diagnostic reagent. Similarly, the plasmin-binding protein may be conjugated to a solid phase support to form a solid phase ("capture") diagnostic reagent. Suitable supports include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, and magnetite. The carrier can be soluble to some extent or insoluble for

the purposes of this invention. The support material may have any structure so long as the coupled molecule is capable of binding plasmin.

In yet another preferred embodiment, Tifapinix or fragments thereof are used for in vivo diagnostic uses. Tifapinix or fragments thereof, i.e. a Kunitz domain that binds very tightly to plasmin can be used for in vivo imaging. Radiolabeled Tifapinix may be administered to a human or animal subject, typically by injection, e.g., intravenous or arterial other means of administration such as subcutaneous, intramuscular in a quantity sufficient to permit subsequent dynamic and/or static imaging using suitable radio-detecting devices. The dosage is the smallest amount capable of providing a diagnostically effective image, and may be determined by means conventional in the art, using known radio-imaging agents as guides. Typically, the imaging is carried out on the whole body of the subject, or on that portion of the body or organ relevant to the condition or disease under study. The radiolabeled binding protein has accumulated. The amount of radiolabeled binding protein accumulated at a given point in time in relevant target organs can then be quantified. A particularly suitable radio-detecting device is a scintillation camera, such as a. gamma. camera. The detection device in the camera senses and records (and optional digitizes) the radioactive decay. Digitized information can be analyzed in any suitable way, many of which are known in the art. For example, a time-activity analysis can illustrate uptake through clearance of the radiolabeled binding protein by the target organs with time. The radioisotope used should preferably be pharmacologically inert, and the quantities administered should not have substantial physiological effect. The binding protein may be radio-labeled with different isotopes of iodine, for example ~~.sup.123 I~~ ^{123}I, ~~.sup.125 I~~ ^{125}I, or ~~.sup.131 I~~ ^{131}I (see, for example, U.S. Pat. No. 4,609,725). The amount of labeling must be suitably monitored.

In applications to human subjects, it may be desirable to use radioisotopes other than ~~.sup.125 I~~ ^{125}I for labeling to decrease the total dosimetry exposure of the body and to optimize the detectability of the labeled molecule. Considering ready clinical availability for use in humans, preferred radiolabels include: ~~.sup.99m Tc~~ ^{99m}Tc, ~~.sup.67 Ga~~ ^{67}Ga, ~~.sup.68 Ga~~ ^{68}Ga, ~~.sup.90 Y~~ ^{90}Y, ~~.sup.111 In~~ ^{111}In, ~~.sup.113m In~~ ^{113m}In, ~~sup. 123 I~~ ^{123}I, ~~sup. 186 Re~~ ^{186}Re, ~~.sup.188 Re~~ ^{188}Re, or ~~.sup.211 At~~ ^{211}At. Radiolabeled protein may be prepared by various methods. These include radio-halogenation by the chloramine-T or lactoperoxidase method and subsequent purification by high

pressure liquid chromatography, for example, see Gutkowska et al in "Endocrinology and Metabolism Clinics of America 16 (1):183, 1987. Other methods of radiolabeling can be used, such as IODOBEADS~~TM~~. Tifapinix or fragments thereof may also be used to purify plasmin from a fluid, e.g., blood. For this purpose, it is preferably immobilized on an insoluble support. Such supports include those also useful in preparing solid phase diagnostic reagents. Proteins can be used as molecular weight markers for reference in the separation or purification of proteins.

Please substitute the following paragraph on page 340, beginning at line 36 through to page 341, line 6:

Sequences within untranscribed or untranslated regions of polynucleotides of the invention may be identified by comparison to databases containing known regulatory sequence such as transcription start sites, transcription factor binding sites, promoter sequences, enhancer sequences, 5'UTR and 3'UTR elements [Pesole et al., (2000) Nucleic Acids Res, 28(1):193-196; http://See Worldwide Website: igs-sever.cnrs-mrs.fr/~gauthere/UTR/index.html]. Alternatively, the regulatory sequences of interest may be identified through conventional mutagenesis or deletion analyses of reporter plasmids using, for instance, techniques described in the section entitled "Identification of Promoters in Cloned Upstream Sequences".

Please substitute the following paragraph on page 343, beginning at line 23:

Proteins or other molecules interacting with a polypeptide of the present invention, can also be found using affinity columns which contain the GENSET protein, or a fragment thereof. The GENSET protein, or a fragment thereof, may be attached to the column using conventional techniques including chemical coupling to a suitable column matrix such as agarose, ~~Affi-Gel®~~ AFFI-GEL, or other matrices familiar to those of skill in art. In some embodiments of this method, the affinity column contains chimeric proteins in which the GENSET protein, or a fragment thereof, is fused to glutathion S transferase (GST). A mixture of cellular proteins or pool of expressed proteins as described above is applied to the affinity column. Proteins or other molecules interacting with the GENSET protein, or a fragment thereof, attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al., (1997), Electrophoresis, 18:

588-598, the disclosure of which is incorporated by reference. Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.